Paroxetine in pregnancy?

FDA advisory flunks as evidence-based medicine

Lawson Wulsin, MD, and Michael Ignatowski, BA

Mrs. J, age 24, has a history of recurrent major depression, for which you have prescribed paroxetine. Newly pregnant, she brings you Internet articles with headlines such as "Depression drugs 'can raise birth defect risks.'"[1] Particularly, the articles mention congenital cardiac defects with paroxetine use during pregnancy. She adds that Web sites offer her legal support and invite her to join class-action lawsuits. How would you respond?

Psychiatrists and patients such as Mrs. J face a dilemma since the FDA requested in December 2005 that GlaxoSmithKline (GSK) change paroxetine's pregnancy warning from category C to category D (see *Related resources*, *page 48*, for the FDA advisory). Selective serotonin reuptake inhibitors (SSRIs) are the antidepressants prescribed most often during pregnancy, and all had been pregnancy class C.[2]

FDA says category D means controlled or observational studies in pregnant women have shown risk to the fetus, but benefits of therapy may outweigh the risk. Category C means adverse effects have been seen in animal studies when no controlled studies in women exist, or studies in women and animals are unavailable (see *Do antidepressants' benefits outweigh the risks?, page 31*).

FDA recommends avoiding paroxetine in women of child-bearing age. How does this advisory change the way we manage depression in pregnancy? How strong is the evidence supporting it?

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SSRIs AND BIRTH DEFECT RISK

Eight prospective or case-control studies of SSRIs in >5,400 pregnant women have been published since 1993 (*Table, page 47*).[3-10] Five included paroxetine.[6-10] The studies ranged from small to large, and none showed a significant increase in major malformations with any SSRI. Even in a study of >2,500 women, no single malformation was overrepresented.[8]

In addition, a recent meta-analysis[11] of 7 prospective comparative cohort studies involving 1,774 pregnant women showed no increased risk of major birth defects from exposure to any of the 8 antidepressants studied, including 4 SSRIs used during the first trimester. The review identified no specific malformation or cluster of malformations associated with first-trimester antidepressant use.

EVIDENCE CITED BY FDA

FDA's advisory (*Box, page 46*) came 3 months after GSK notified health professionals that fetuses exposed to paroxetine during organogenesis may be at increased risk of developing malformations, particularly ventricular septal defect (see *Related resources*).

continued

Box

Paroxetine in pregnancy: What FDA recommends to you and your patients

The FDA is awaiting the final results of the recent studies and accruing additional data related to the use of paroxetine in pregnancy in order to better characterize the risk for congenital malformations associated with paroxetine. In the interim, FDA recommends the following:

Physicians who are caring for women receiving paroxetine should alert them to the potential risk to the fetus if they plan to become pregnant or are currently in their first trimester of pregnancy. Discontinuing paroxetine therapy should be considered for these patients. In individual cases, the benefits of continuing paroxetine may outweigh the potential risk to the fetus. If the decision is made to discontinue paroxetine and switch to another antidepressant or cease antidepressant therapy, paroxetine discontinuation should be undertaken only as directed in the prescribing information. Paroxetine should generally not be initiated in women who are in their first trimester of pregnancy or in women who plan to become pregnant in the near future.

Women who are pregnant, or planning a pregnancy, and currently taking paroxetine should consult with their physician about whether to continue taking it. Women should not stop the drug without discussing the best way to do that with their physician.

Source: Verbatim from FDA advisory, December 2005.

GSK's study. GSK conducted a retrospective cohort study of major congenital malformations in children of women who had taken antidepressants in the first trimester.[12] The study used data from two Ingenix databases of United HealthCare medical insurance information. Malformation rates were compared with those in the general population, as determined by a 1999 Centers for Disease Control and Prevention study of four pregnancy registries and a population-based birth-defect surveillance system.[13] After adjustments were made for other antidepressants and known teratogenic drugs the women took while pregnant, the study showed:

- Major congenital defects occurred in 4% of 527 pregnancies during which women used paroxetine, (adjusted odds ratios [OR], 2.20; 95% CI, 1.34-3.63), compared with 3% prevalence in the general population.
- Cardiovascular malformations occurred at an adjusted rate of 2% (OR, 2.08; 95% CI, 1.03-4.23), compared with 1% in the general population.
- 10 of the 14 cardiovascular malformations were ventricular septal defects.

The cardiovascular malformation rate associated with paroxetine was significantly higher than the rates seen with other SSRIs examined in the databases.

The GSK investigation was an unpublished retrospective study without peer review when FDA issued its advisory about paroxetine.

Two abstracts. The FDA alert also cited two abstracts that were not peer-reviewed and whose findings were inconsistent with those of GSK.

In the first abstract, a U.S. case-control study showed an increased risk of major malformations in 5,357 infants of women who took SSRIs in the first trimester, compared with 3,366 normal controls.[14] Specific birth defects included:

- 161 infants with omphalocele (bowel protrusion through an abdominal wall defect) (OR, 3.0; 95% CI, 1.4-6.1)
- 372 infants with craniosynostosis (deformities caused by premature closure of skull sutures) (OR, 1.8; 95% CI, 1.0-3.2).

Paroxetine was associated with an increased risk of omphalocele (OR, 6.3; CI, 2.0-19.6) but

Table

8 published studies: No significant increase in birth defects with SSRIs

Year/location	Authors	Study design	SSRI exposure (# of patients)	Risk of major malformation
1993/USA, Canada	Pastuszak et al[3]	Prospective cohort, controlled	Fluoxetine (98)	SSRI: 2% Control: 1.8% (ns)
1996/USA	Chambers et al[4]	Prospective cohort, controlled	Fluoxetine (174)	SSRI: 3.4% Control: 2.7% (ns)
1997/ worldwide	Goldstein et al[5]	Clinical trial	Fluoxetine (28)	SSRI: 3.6% (ns)
1998/USA, Canada, Brazil	Kulin et al[6]	Prospective cohort, controlled	Paroxetine (97) Sertraline (147) Fluvoxamine (26)	Total SSRI: 4.1% Control: 3.8% (ns)
1999/Sweden	Ericson et al[7]	Case-control	Citalopram (364) Paroxetine (118) Sertraline (32) Fluoxetine (15)	Citalopram: 3.9% Total risk of remaining SSRIs: 3.8% (ns)
2002/USA	Simon et al[9]	Case-control	Fluoxetine (129) Sertraline (32) Paroxetine (28)	Total SSRI: 6.5% Control: 4.9% (ns)
2003/USA	Hendrick et al[10]	Prospective, uncontrolled	Fluoxetine (13) Paroxetine (19) Sertraline (36)	Total SSRI:1.4% (ns)
2005/Sweden	Hallberg et al[8]	Case-control	Citalopram (1,696) Paroxetine (708) Sertraline (1,067) Fluoxetine (574)	Citalopram: 3.1% Paroxetine: 3.4% Sertraline: 2.0% Fluoxetine: 3.3% (ns)

ns: No statistically significant difference

no significant risk of cardiovascular defects. The authors stated that the associations need to be confirmed in other data sets, but this had not been done when FDA issued its warning.

In the second abstract, Wogelius et al[15] examined a Danish prescription database and found a slightly increased risk for congenital malformation (OR, 1.4; 95% CI, 1.1-1.9) and specifically cardiac malformation (OR, 1.6; 95% CI, 1.0-2.6) with SSRIs during pregnancy. This study included 1,054 women who filled SSRI prescriptions within a window of 30 days before conception to the end of the first trimester. The authors compared these malformation rates with those in 150,908 controls (women who did not fill an SSRI prescription in this period before and during pregnancy).

This cohort study did not report specific data about paroxetine, nor whether the women took the SSRIs they acquired.

continued

Related resources

- GlaxoSmithKline letter to clinicians about paroxetine during pregnancy, September 2005. www.fda.gov/medwatch/safety/2005/Paxil_dearhcp_letter.pdf
- Food and Drug Administration advisory on paroxetine during pregnancy, December 2005 (full text). www.fda.gov/cder/drug/advisory/paroxetine200512.htm.

DRUG BRAND NAMES

Citalopram • Celexa
Fluoxetine • Prozac
Fluvoxamine • Luvox
Paroxetine • Paxil, Paxil CR, Pexeva
Sertraline • Zoloft

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Epidemiologic studies. The FDA also cited two unpublished epidemiologic studies.

The first analyzed a Swedish national registry database and found that infants whose mothers received paroxetine in early pregnancy had a 2% risk of cardiac defect, compared with a 1% risk among all registry infants. Although the FDA advisory does not cite a reference, the data may be from the same registry in which previous studies have shown no significant difference in malformations when comparing paroxetine-exposed infants with controls.[7,8]

The second epidemiologic study used a U.S. insurance claims database and found that infants of women who received paroxetine in early pregnancy had a 1.5% risk of cardiac defect, compared with 1% among infants whose mothers took other antidepressants.

What do you think?

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Unfortunately, FDA has refused to release information about these studies beyond what it gave in the advisory, stating simply that the studies are unpublished. Evidence-based medicine can be difficult to practice if clinicians can't access the evidence to assess its quality.

IN CLINICAL PRACTICE

Evidence from five peer-reviewed, published studies contradict the FDA advisory on increased risk for congenital cardiac malformations with paroxetine use during pregnancy. So, when prescribing antidepressants for depressed pregnant women, do we rely on the five negative studies or practice defensive medicine and choose SSRIs other than paroxetine?

We have good reasons to question the FDA advisory's scientific validity, but our patients—and our lawyers—will be more comfortable if we avoid paroxetine in women of child-bearing potential for now. Excluding paroxetine and relying on other SSRIs when necessary to treat major depression during pregnancy is hardly evidence-based medicine, but it's a legitimate practice of legally-defensive medicine.

This answers our question about how to respond to Mrs. J's concerns:

- First, she and I would decide if she needs an antidepressant during pregnancy.
- Then, after reviewing with her the FDA warning on paroxetine and discussing its questionable scientific validity, I would recommend that she switch to another SSRI.
- If she chooses to continue paroxetine, I would ask her to sign the note that documents our discussion of the pros and cons of choosing paroxetine instead of alternatives.

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Continued brief summary of prescribing information from previous page.

Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules

Adverse Events in Clinical Studies with Focalin™ XR – Adults

Adverse Events Associated with Discontinuation of Treatment: In the adult placebo-controlled study, 10.7% of the Focalin XR-treated patients and 7.5% of the placebo-treated patients discontinued for adverse events. Among Focalin XR-treated patients, insomnia (1.8%, n=3), feeling jittery (1.8%, n=3), anorexia (1.2%, n=2), and anxiety (1.2%, n=2) were the reasons for discontinuation reported by more than 1 patient.

Adverse Events Occurring at an Incidence of 5% or More Among Focalin™ XR-Treated Patients: Table 2 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in adults with ADHD at fixed Focalin XR doses of 20, 30, and 40 mg/day. The table includes only those events that occurred in 5% or more of patients in a Focalin XR dose group and for which the incidences in patients treated with Focalin XR appeared to increase with dose. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 2
Treatment-Emergent Adverse Events[1] Occurring During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
No. of Patients with AEs				
Total	84%	94%	85%	68%
Primary System Organ Class/ Adverse Event Preferred Term				
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

[1]Events, regardless of causality, for which the incidence was at least 5% in a Focalin XR group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

Two other adverse reactions occurring in clinical trials with Focalin XR at a frequency greater than placebo, but which were not dose related were: Feeling jittery (12% and 2%, respectively) and Dizziness (6% and 2%, respectively).

Table 3 summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of Focalin XR in the treatment of ADHD.

Table 3
Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

Adverse Events with Other Methylphenidate HCl Dosage Forms

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include: ***Cardiac:*** angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia; ***Gastrointestinal:*** abdominal pain, nausea; ***Immune:*** hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura; ***Metabolism/Nutrition:*** anorexia, weight loss during prolonged therapy; ***Nervous System:*** dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis; ***Vascular:*** blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate: ***Blood/Lymphatic:*** leukopenia and/or anemia; ***Hepatobiliary:*** abnormal liver function, ranging from transaminase elevation to hepatic coma; ***Psychiatric:*** transient depressed mood, aggressive behavior; ***Skin/Subcutaneous:*** scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Poison Control Center

The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

Recommended Treatment

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of dexmethylphenidate from Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis for Focalin overdosage has not been established.

Store at 25°C (77°F), excursions permitted 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]

Dispense in tight container (USP).

Focalin™ XR is a trademark of Novartis AG
SODAS® is a trademark of Elan Corporation, plc.

This product is covered by US patents including 5,837,284, 5,908,850, 6,228,398, 6,355,656, and 6,635,284.

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For legal reasons alone, avoid using paroxetine in women of child-bearing potential unless their depressive symptoms respond exclusively to this medication. Document all risk-benefit discussions you have with patients about SSRI use during pregnancy.

Bottom Line